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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/225,718	01/06/1999	DOUGLAS A. TRECO	07236/013004	1979

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EXAMINER
KETTER, JAMES S

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No. 09/225,718	Applicant(s) TRECO ET AL.	
	Examiner James S. Ketter	Art Unit 1636	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 16 April 2002 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *16 April 2002*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☐ affidavit, b)☒ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☐ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: none

Claim(s) objected to: none

Claim(s) rejected: 114-168

Claim(s) withdrawn from consideration: 66-113

8.☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☐ Other: _____

Continuation of 5. does NOT place the application in condition for allowance because of the following reasons: At page 3 and 4 of the amendment after final, Applicants argue that the invention has been misunderstood--that delivery of modified cells to the patient is encompassed, not nucleic acid directly. However, this is and was understood. The comparison between administration of proteins and administrations of nucleic acids directly was discussed in the sense that the nucleic acid is delivered, albeit indirectly. It should be noted that transfection of a cell, followed by implantation of that cell into the patient is even more technicaly divergent from direct delivery of a protein, and thus prior art with respect to deleivery of proteins becomes even less applicable to the question of enablement. Applicants then argue that no explanation was given why it was found that trial-and-error experimentation would have been required. However, such reasons are of record. In Verma et al., for example, at page 240, at the paragraph bridging the center and right columns, it is taught that trail-and-error experimentation would be required to find an expression construct which would permit long term expression of any particular gene.

Applicants then cite the example in the art of adjusting the amount of parathyroid tissue in a patient. However, it is not clear that such was practiced prior to the effective filing date of the invention. Even if it were routine, it is noted that such a procedure uses cells which are not genetically altered. The predictability and persistence of expression of the rcombinant construct is certaily at issue in the present rejection. Further, this stands as one procedure in one tissue type. Whether such procedures are routine in general is not clear.

At pages 5 and 6, Applicants argue that they demonstrated long term exprssion of EPO in mice. However, these were immune-compromised animals, which do not represent a good model system for humans with normal immune systems. Indeed, as noted of record previously, Orkin et al. taught that animal models were not recognized as representative model systems for humans in this art. Applicants go on to argue that "expression in ex vivo therapies is not necessarily transient." However, this statement makes clear that such expression sometimes is transient.

At the next paragraph, Applicants argue that Phase I clincal trials have shown some positive results for Factor VIII expression. However, it is not clear whether the protocols employed in the recited trial would have been practiced by the skilled practitioner at the time of filing of the invention. If trial-and-error had been employed to develop the protocol used, then whatever success the trial evinced would be considered the product of a degree of experimentation which would have been regarded as undue under 35 USC 112, first paragraph. Furthermore, the trial represents a single experiment. Such is not commensurate in scope with the (much broader) claimed invention. Success in one attempt does not provide evidence of a routine nature of the experimentation required to practice the invention as claimed, particularly at the time of filing.

At the paragraph bridging pages 6 and 7, Applicants argue that they are not aware of nown problems with persistence of expression in ex vivo gene therapy. Applicants cite Ferber, which teaches that failure in gene therapy to achieve long term expression is "in part" due to lack of placing the gene into the genome of the host cell. However, it is apparent even from this recent teaching that non-integration or non-targetting has been only part of the problem with achieving success in the art of gene therapy. Further along, Ferber quotes Kay as saying that "the persistnce issue is being solved." This is as of 2001, and still does not indicate that gene therapy is routine, even with integration as Ferber discusses and teaches.

At page 7, Applicants ague that Verma et al. taught an experiment in mice where Factor IX was expressed for a long period of time. However, Verma et al. goes on to teach that finding other combinations of expression systems and genes would be "trial-and-error." This is a broadly relevant comment on the unpredictability of the art, Applicants' owm experimental results (noted supra) notwithstanding.

Applicants questions why the Examiner "continues to cite Orkin [sic]", as though time has diminished the validity of its comment upon the art of gene therapy. However, Orkin et al. was published well after the effective filing date of the present invention, and represents evidence as to the state of the art at the time of and even after the filing of the invention.

Applicants attack the Anderson reference as not being applicable to ex vivo methods. However, Anderson is drawn to both in and ex vivo gene therapy, as is clear from the teachings of the paper in general. With respect to the therapeutic trial taught ni Anderson and noted by Applicants, Anderson found tha "no definitive conclusion" could be drawn about the effectiveness of the gene therapy, because of the other therapy being continuously applied.

Applicants argue that Table 4 of Mountain does not apply to ex vivo methods. However, Mountain does not specify. Indeed, the entire Mountain reference is drawn to both in and ex vivo. There is no reason to think that Table 4 does not comment upon ex vivo methods. Applicants then point to two post-filing date references noted by Mountain in which long term expression was demonstrated. However, these method merely demonstrated gene expression at some level, of a marker gene, in an animal model system. Furthermore, the methods used in these references were not those of the instant claims. To have gone from Applicants' disclosure in the context of the art to the methods disclosed in said references would have required significant modification of the disclosed methods. It is maintained that such would have required undue experimentation.

Finally, Applicants conclude by asking why an enablement rejection has ben based on the question of persistence of expression, arguing that short term expression can be useful. However, the inability to provide consistant, predictable, long term expression precludes the practice the invention for the types of conditions generally contemplated in the specification. Furthermore, lack of persistent expression is only one issue in the present rejection. Selection of disease conditions to treated, and protocols which thus provide proper levels of gene products or secondary products to be therapeutic has also been discussed. Applicants have focussed on certain factors more than others in their previous remarks, and this has guided the direction of the rebuttals offred thereto.

JAMES KETTER
PRIMARY EXAMINER